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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
JUEDES, AMY E	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 04/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/006,797	FRASER ET AL.	
	Examiner	Art Unit	
	Amy E. Juedes, Ph.D.	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-18 and 21-38* is/are pending in the application.

4a) Of the above claim(s) *7-9,14,17,18 and 21-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,10,11,13,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 4/10/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment and remarks, filed 2/13/06, are acknowledged.

Claims 1-2 and 6 have been amended.
Claim 12 has been cancelled.
Claims 1-11, 13-18, and 21-38 are pending

2. Applicant has traversed the withdrawal of claims 5, 7-9, and 14 as being drawn to non-elected species. The traversal is on the ground(s) that Claim 5 merely specifies bacteria from which the targeting molecule is derived, and that claims 7-9 and 14 depend from elected claim 6 and specify variants of the elected APC targeting molecule. Since the elected targeting molecule, SPE-C is derived from Staphylococcus pyogenes, Claim 5 has been rejoined. However, Applicant's arguments with regard to claims 7-9 and 14 are not persuasive. Applicant states that the elected species is listed in claim 6, i.e. an APC targeting molecule derived from SPE-C. However, in the reply to the restriction requirement filed on 12/9/04, Applicant elected SPE-C as the specific species of targeting molecule. Thus, Applicant has elected a targeting molecule comprising a wild-type SPE-C lacking a fully functional T-cell receptor binding site. Therefore, the other specific variants of SPE-C recited in claims 7-9 and 14 are non-elected species that have been properly withdrawn from examination.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 17-18 and 21-38 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 7-9 and 14 stand withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected species.

Claims 1-6, 10-11, 13, and 15-16 are being acted upon.

4. The objections to the amendment of 4/5/02 are withdrawn in view of Applicant's submission of a marked-up version of the amendment. However, the amendment to the claims on 12/4/01 is objected to. A marked-up copy of the amendment is required.

5. The rejection of claim 12 for lack of enablement is withdrawn in view of Applicant's cancellation of the claim.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-4, 6, 10-13, and 15-16 stand rejected and claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As set forth previously, A) The terms "immunomodulator" and "immunomodulatory" in claims 1-2 are indefinite because it is ambiguous as the direction (positive or negative) or degree of said immunomodulator. The terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. As claims 3-4, 6, 10-13, and 15-16 depend on claim 1, and do not clarify the indefiniteness of the invention, they are also rejected.

B) Additionally, the terms "fully functional" in Claim 1 and "little or no ability" in Claim 2 are relative terms which render the claims indefinite. The terms are not defined by the claim or the specification, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the metes and bounds of the invention. The recitation "little" as pertaining to ability of a superantigen to activate T cells is vague. It is known that disruption of superantigen T cell receptor binding sites can result in reduced ability to stimulate only certain subsets of T cells, while being fully functional to stimulate other subsets (see Kappler et al., p391, paragraph 4). It is unclear whether a superantigen with such a disruption might reasonably be considered to have a "little" ability to activate T cells. Furthermore, disruption of the T cell receptor binding site may result in a wide range of effects on the ability of a superantigen to stimulate T cells (see Kappler et al. Fig. 4-6). For example, a disruption that results in a 10,000 fold reduction in T cell stimulatory capacity (as disclosed for SMEZ-2 D42N of the instant application) would be considered to have "little" ability to activate T cells. However, it is not defined by the claim or the specification if a modification that resulted in, for example, only a 2 fold reduction might also be considered to have "little" ability to activate T cells. Furthermore, the recitation of "fully functional T cell receptor binding site" in Claim 1 is indefinite. Since a superantigen can bind T cells and/or stimulate T cells, it is unclear if the term "functional" relates to either or both of those functions. Likewise, the term "fully" is vague. It is not clear what degree of impairment is necessary to be considered not fully functional. Therefore, the claims as written do not define the metes and bounds of the invention. As claims 6, 10-13, and 15-16 depend on claim 1, and do not clarify the indefiniteness of the invention, they are also rejected.

C) Additionally, the term "non-immunogenic" in Claim 13, as pertaining to an immunomodulatory antigen is indefinite. It is unclear how an antigen can be both immunomodulatory (i.e. capable of positively or negatively stimulating an immune response) and also non-immunogenic (i.e. not capable of stimulating an immune response.

Applicant's arguments, filed 2/13/06, have been fully considered but they are not persuasive.

With regard to A), Applicant argues that the specification teaches both the "direction" and "degree" of the "immunomodulator" and "immunomodulatory antigen". Applicant specifically cites pg. 1 of the specification which discloses that immunomodulatory constructs can be used to enhance or suppress an immune response. It is noted that the generic discussion cited by Applicant cannot be considered adequate to define the direction or degree of immunomodulation required by the claims.

Applicant also cites pg. 7 of the specification which discloses peptides that can be immunostimulatory or immunosuppressive. However, a discussion of the properties of peptides cannot be considered an adequate definition of the metes and bounds of the much broader terms "immunomodulator" and "immunomodulatory antigens".

Applicant also cites pg. 6 and 24 of the specification which disclose that a preferred use or specific embodiment of the invention is to enhance responses to synthetic peptides. These specific examples cannot be considered an adequate definition of the terms "immunomodulator" or "immunomodulatory antigen".

Applicant further argues that those skilled in the art would understand the scope of claims 1 and 2 when read in light of the specification. However, as discussed above, the specification fails to specifically define the terms "immunomodulator" or "immunomodulatory antigen". Additionally, it is unclear how the invention can be both simultaneously capable of enhancing and suppressing (i.e. modulating) an immune response, since these are mutually exclusive possibilities. Thus, the metes and bounds of the claims cannot be established.

With regard to B), Applicant argues that a T cell receptor binding domain of a superantigen is well known in the art, and that one skilled in the art would know what a superantigen without a "fully functional T cell receptor binding site" or a superantigen that has "little or no ability to activate T cells" encompasses. This is not found persuasive. While it may be true that a T cell receptor binding site of a superantigen is well

known in the art, the degree of functionality of said binding site as recited in the claims is still ambiguous. For example, disruption of said binding site might disrupt binding or the ability to stimulate only certain subsets of T cells and not others, would this be considered not "fully" functional or having "little" ability to stimulate T cells? On the other hand, it is possible that the claims require that the superantigen not be able to bind to or stimulate any T cells.

Applicant further argues that the acceptability of the claim language depends on whether one of ordinary skill in the art would understand what is claimed in light of the specification. Applicant specifically cites pg. 2-3 and pg. 16 of the specification. However, it is noted that Applicant has cited a generic discussion of the properties of the T cell receptor binding domain of a superantigen, and a specific example of a mutated superantigen. These cites do not clarify what types of superantigen are encompasses by the claims. In fact, the instant specification does not define what is meant by "fully functional" or "little or no" ability to activate T cells at all. Therefore, the metes and bounds of the claims cannot be established.

With regard to C), Applicant argues that it is well known that certain antigens are themselves non-immunogenic and that the claims encompass antigens that are non-immunogenic when not coupled to the targeting molecule. However, claim 1 is limited to coupling "immunomodulatory" antigens to a targeting molecule. While other non-immunomodulatory antigens may well be non-immunogenic, the instant claims are specifically limited to immunomodulatory antigens. It is the examiners position that an immunomodulatory antigen cannot be non-immunogenic, as claimed. Thus, the claims are rendered indefinite.

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1–4, 11-13, and 15-16 stand rejected and claim 5-6 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims

contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

As set forth previously, Applicant has not adequately disclosed that they are in possession of APC-targeting molecules that "mimic" a superantigen or that are "structurally" a superantigen.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species, by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. (See Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, especially page 1106 3rd column). A "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. MPEP 2163 II.A.3a.ii.

In the instant case, Applicant is in possession of specific APC targeting molecules that are mutated superantigens, as disclosed in Table 2 of the instant specification. However, Applicant has not adequately disclosed that they are in possession of APC-targeting molecules that "mimic" a superantigen or that are "structurally" a superantigen. For example, an antibody which is specific for MHC-II could be considered a mimic of a superantigen or structurally a superantigen (i.e. binds to MHC-II, and contains an MHC-II binding region). Thus, Applicant has only disclosed a limited number of APC targeting molecules. It does not appear based upon the limited disclosure that Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the limited number of species disclosed and the extensive variation permitted within the genus of "mimics a superantigen" or "structurally a superantigen."

Applicant's amendment is sufficient to overcome the rejection as it pertains to APC-targeting molecules that "mimic" a superantigen. However, Applicant's arguments filed 2/13/06 are not persuasive relating to APC-targeting molecules that are "structurally" a superantigen or "contain a part" of a superantigen.

Applicant argues that the meaning of an APC targeting molecule which is structurally a superantigen is well known in the art. Applicant further states that it refers to a polypeptide sharing a structural element with another polypeptide (a superantigen), i.e. an amino acid sequence. However, it is noted that polypeptides sharing an amino acid sequence with a superantigen, as argued by Applicant, encompasses a broad range of polypeptides. For example, the claims encompass any polypeptide that shares any degree of

sequence similarity with a superantigen. This might include peptide fragments of a superantigen, or any mutated, substitution, or deletion of a superantigen. The only limitation of the claims is that the superantigen does not comprise a T cell receptor binding site. Thus, the claims might even include small peptides of superantigens that may not even function to bind to MHC or be capable of functioning as "immunomodulators". The same is true for amended claim 1 which now encompasses APC-targeting molecules that "contain a part of a superantigen which does not include a fully functional T-cell receptor binding site". Therefore, the genus encompassed by APC targeting molecules that "contain a part of a superantigen" or "are structurally a superantigen" is extremely large, and might encompass a broad range of different peptides that are structurally different (i.e. comprise unique sequences). In contrast, Applicant has only disclosed a limited number of APC targeting molecules that are very similar in that they all comprise an MHC binding site. Thus, it is clear that Applicant is not in possession of the claimed genus of targeting molecules.

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1—4, 11-13, and 15-16 stand rejected and claim 5 is rejected under 35 U.S.C. 102(b) as being anticipated by Yamoaoka e al, 1998, Infection and Immunity, vol. 66 pp. 5020-5026.

As set forth previously, Yamaoka teaches a mutated superantigen that has a disrupted/non-fully functional T cell receptor binding site (see materials and methods). Said mutated superantigen is coupled to an antigen (GST, see pg 5022 paragraph 1) and can act as an immunomodulator, in that it can weakly stimulate peripheral blood lymphocytes (see fig. 2). Furthermore, said mutated superantigen is derived from SPE-C, (see pg. 5020, materials and methods). Claim 3 is included since the superantigen was mutated by amino acid substitution. Claim 4 is included since the T cell receptor binding site of the superantigen has been deleted (i.e. is non-functional and therefore not present). Claim 10 and 11 are included since Yamaoka teaches that the superantigen is reversibly coupled to a protein (GST can be cleaved off - see pp. 5022 paragraph 1). Claims 15-16 have been included since the reference teaches using the mutated superantigen in vivo (i.e. as a pharmaceutical composition or vaccine - see fig. 2, and pg. 5023).

Applicant's arguments filed 2/13/06 have been fully considered but they are not persuasive.

Applicant argues that the GST protein taught by Yamoaoka is not an immunomodulatory antigen, since GST interferes with binding to MHC class 2 protein during antigen presentation. However, Applicant has not provided any evidence, but merely speculated that GST interferes with antigen presentation. Moreover, even if GST does in fact have such a property, this would only further support the examiners contention that GST is in fact an immunomodulatory antigen, since interfering with antigen presentation can be considered an "immunomodulatory" property. Additionally, GST is well known in the art as an antigen (for example, monoclonal antibodies can be raised against GST, see Yan et al., 1996). The fact that GST can induce an immune response makes it an "immunomodulatory antigen", as claimed.

9. The following are new grounds of rejection.

10. Claims 1-6, 10-11, 13, and 15-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the instant specification does not enable one of ordinary skill in the art to make and use an immunomodulator containing "a part of a superantigen" or a molecule which is "structurally a superantigen", as broadly claimed.

The specification disclosure is insufficient to enable one skilled in the art to practice the invention as claimed without an undue amount of experimentation. Undue experimentation must be considered in light of factors including: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill in the art, the level of predictability of the art, the amount of direction provided by the inventor, the existence of working examples, and the quantity of experimentation needed to make or use the invention, see *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).

In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA

1970) states, "The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art." "The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling" (MPEP 2164.03). The MPEP further states that physiological activity can be considered inherently unpredictable. With these teachings in mind, an enabling disclosure, commensurate in scope with the breadth of the claimed invention, is required.

The specification provides insufficient guidance to enable one of ordinary skill in the art to make and use the immunomodulator as broadly claimed. The instant claims are drawn to an immunomodulator comprising an APC targeting molecule that is "structurally" or "contains a part" of a superantigen. Note that that molecules that are "structurally" a superantigen encompasses any polypeptides sharing any amino acid sequence with a superantigen. This encompasses peptide fragments, or any mutated, substituted, or deleted superantigen sequence. Likewise, the same broad genus of superantigen fragments is encompassed by claims drawn to an APC targeting molecule that "contains a part of a superantigen". The only limitation of the instant claims is that the superantigen does not comprise a T cell receptor binding site. Superantigens are well known in the art to stimulate immune cells via their ability to bind to MHC and T cell receptor. (see Hong-Gellar et al., pg. 93 in particular). However, the instant claims encompass, in their breadth, superantigen fragments that neither bind to a T cell receptor or to MHC. Since superantigens do not have any known ability to bind to APC structures other than MHC, it is unclear how superantigen fragments without an MHC binding site would be able to act as APC targeting molecules or immunomodulators, as broadly claimed. Furthermore, all of the examples provided in the instant specification utilize superantigens with only a specific deletion/mutation in the T cell receptor binding site, but which maintain a fully functional MHC binding site. Therefore, the instant specification does not provide sufficient

guidance that would enable one of ordinary skill in the art to make or use the immunomodulator which contains "a part" or is "structurally" a superantigen, as broadly claimed. Accordingly, undue experimentation is required in order to make and use the claimed invention.

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy E. Juedes, Ph.D. whose telephone number is 571-272-4471. The examiner can normally be reached on 8am - 5pm, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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April 5, 2006

4/8/06
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